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(21) International Application Number: PCT/US97/10517 (22) International Filing Date: 17 June 1997 (17.06.97)		(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	
(30) Priority Data: 60/020,166 21 June 1996 (21.06.96) US 60/020,165 21 June 1996 (21.06.96) US 9614943.0 16 July 1996 (16.07.96) GB 9614942.2 16 July 1996 (16.07.96) GB		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
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(54) Title: VACCINES COMPRISING SYNTHETIC GENES			
(57) Abstract <p>Synthetic polynucleotides comprising a DNA sequence encoding a peptide or protein are provided. The DNA sequence of the synthetic polynucleotides comprise codons optimized for expression in a nonhomologous host. The invention is exemplified by synthetic DNA molecules encoding HIV <i>env</i> as well as modifications of HIV <i>env</i>. The codons of the synthetic molecules include the projected host cell's preferred codons. The synthetic molecules provide preferred forms of foreign genetic material. The synthetic molecules may be used as a polynucleotide vaccine which provides immunoprophylaxis against HIV infection through neutralizing antibody and cell-mediated immunity. This invention provides polynucleotides which, when directly introduced into a vertebrate <i>in vivo</i>, including mammals such as primates and humans, induces the expression of encoded proteins within the animal.</p>			

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/10517

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/49 A61K48/00 A61K31/70 C12N15/67

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 20660 A (UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER) 3 August 1995 see page 45, line 16 - page 62, line 10 ---	1-13, 15-18
X	K. OKUDA ET AL.: "Induction of potent humoral and cell-mediated immune responses following direct injection of DNA encoding the HIV typr 1 env and rev gene products" AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 11, no. 8, August 1995, pages 933-943, XP002036839 see the whole document --- -/-	1-13, 15-18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

5 December 1997

Date of mailing of the international search report

20.01.98

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/10517

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B. WANG ET AL.: "Gene inoculation generates immune responses against human immunodeficiency virus type 1" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 90, 1 May 1993, WASHINGTON US, pages 4156-4160, XP000608482 see the whole document ---	1-13, 15-18
X	WO 94 16737 A (D.B. WEINER ET AL.) 4 August 1994 see page 59, line 26 - page 89, line 22 ---	1-13, 15-18
P,X	WO 96 21356 A (VANDERBILT UNIVERSITY) 18 July 1996 see the whole document ---	1-13, 15-18
P,X	WO 97 11086 A (THE GENERAL HOSPITAL CORPORATION) 27 March 1997 see page 16, line 19 - page 17, line 15 ---	1-3,5,19
P,X	DATABASE WPI Section Ch, Week 9641 Derwent Publications Ltd., London, GB; Class B04, AN 96-408330 XP002036840 & JP 08 198 774 A (OKUDA K) , 6 August 1996 see abstract ---	1-13, 15-18
E	WO 97 31115 A (MERCK & CO., INC.) 28 August 1997 see the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/10517

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 6-8, 10-12, and 14-18
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
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of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
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restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 97/10517

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9520660 A	03-08-95	CA 2181832 A EP 0740704 A JP 9508622 T US 5620896 A	03-08-95 06-11-96 02-09-97 15-04-97
WO 9416737 A	04-08-94	US 5593972 A AU 675702 B AU 6232094 A EP 0681483 A HU 73099 A JP 8509694 T ZA 9400493 A	14-01-97 13-02-97 15-08-94 15-11-95 28-06-96 15-10-96 03-01-95
WO 9621356 A	18-07-96	AU 2958795 A	31-07-96
WO 9711086 A	27-03-97	NONE	
WO 9731115 A	28-08-97	AU 2124697 A	10-09-97